REMARKS/ARGUMENTS

It is noted that Box 10 of the Office Action Summary (PTOL-326) pertaining to the drawings has not been checked and applicants will therefore proceed on the assumption that the drawings on file are acceptable.

Claim 13 has been objected to because of the misspelling of "cysteine." In response, the spelling of that word has been corrected.

Turning to the merits, claim 11 stands rejected under 35 USC 103(a) as being unpatentable over Burtin et al. U.S. Patent No. 6,248,238 ('238), the Examiner reasoning that '238 discloses medical apparatus for the treatment of blood or plasma comprising a semipermeable membrane having an anti-protease agent bound to it by an ionic interaction with the electronegative sites of the membrane, apparently concluding that this coupling is "via functional groups." The Examiner concedes that '238 differs from the claimed invention in that it does not expressly disclose a device comprising four such membranes, but concludes that it would have been obvious to one of ordinary skill in the art to have used multiple membranes in the '238 apparatus in order to ensure thorough treatment of blood or plasma. The Examiner further contends that, since all the structural limitations described in claim 11 are rendered obvious by '238, "the invention renders obvious the intended use of removing proteases from biological fluids and pharmaceutical solutions." This rejection is respectfully traversed for the following reasons.

Initially, the last-quoted phrase is not understood. Specifically, what is "the invention" referred to by the Examiner? The subject matter of '238 or the claimed invention? In the event this rejection is maintained, clarification is respectfully requested.

Addressing the merits, there is a fundamental scientific error in the Examiner's position. That error is the Examiner's misuse of the term "functional group" so as to include electrostatic or ionic bonding, which is the form of bonding of the anti-protease agent to the membrane described by '238. See '238 at column 4, lines 35-45 and 53-56 and in the Examples, whereby it is made very clear that the semi-permeable membrane is first electrostatically charged with a negative charge and then a cationic (or positively charged) anti-protease agent is coated onto the membrane, the bonding taking place between such oppositely charged components. See also the enclosed printout from the on-line encyclopedia *Wikipedia*, showing the accepted conventional organic chemistry definition of "functional groups." Moreover, independent claim 11 has been amended so as to specify that the protease inhibitor is coupled by a nonionic chemical bond to the membrane body via the functional groups. Without more, claim 11 is respectfully submitted to be nonobvious relative to '238.

Claims 11-15 stand rejected under 35 USC 103(a) as being unpatentable over Nussbaumer et al. U.S. Patent No. 6,294,090 ('090) in view of Nemori et al. U.S. Patent No. 7,067,272 ('272) and Bergmann U.S. Patent No. 5,168,041 ('041), the Examiner reasoning that '090 discloses an adsorptive separation device having multiple adsorption membranes with different adsorption properties that is capable of selective separation of enzymes from media, that '272 discloses thin membranes comprising a protease inhibitor for inhibiting matrix metalloproteinase or serine protease or cysteine protease, and that it would have been obvious to a person of ordinary skill in the art to have used the '272 membranes in the '090 separation device in order to remove proteases from fluids. The Examiner concedes that '272 does not expressly teach that the protease inhibitors are chemically coupled to functional groups in the

membrane, but contends that "it would have been obvious that such is occurring in order for the protease inhibitors to be bound to the Nemori ['272] thin membranes." The Examiner further concedes that neither '090 nor '272 disclose the use of different protease inhibitors in multiple adsorption membranes or the use of two different protease inhibitors in a single membrane or that protease inhibitors may be any of the compounds recited in applicants' claim 13, but contends that '041 lists various protease inhibitors in Table 1 that include pepstatin, bestatin, leupeptin and p-aminobenzamidine, and that therefore it would have been obvious to a person of ordinary skill in the art to use such protease inhibitors "in the membranes of the device," presumably referring to the '090 separation device. This rejection is respectfully traversed as well for the following reasons.

The Examiner is respectfully submitted to have oversimplified and unduly broadened the teachings of both secondary references '272 and '041. Specifically, with respect to '272, the Examiner appears to have overlooked that the device in question utilizes protease activity-measuring membranes, an essential component of which is a protease substrate of either a transferrin or albumin derivative that is crosslinked with a hardening agent. The mechanism the '272 device uses for the detection of protease in the biofluid in question is that the protease in the biofluid digests the protease substrate by enzymatic degradation, thereby showing the relative degree of concentration of protease in the biofluid. Nowhere in '272 is it stated exactly what the function of the protease inhibitor is, and, more importantly, that the protease inhibitor is bound to the '272 membranes. In this connection it is noted that the Examiner has assumed that protease inhibitors of '272 are in fact bound to the membranes; in the event the Examiner persists in this

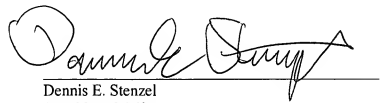
contention, he/she is respectfully requested to point out precisely where in the text of '272 this is supported.

As to '041, the Examiner appears to have entirely overlooked the context in which the list of protease inhibitors found in Table 1 of that patent appears. Specifically, the entire thrust of '041 has nothing to do with the removal of proteases from serum or plasma, the object of the invention instead being the determination of the amount of the human bone protein osteocalcin in serum or plasma. See '041 at column 1, lines 5-44. This determination is made by way of an immunoassay involving the breakdown of osteocalcin 37-49 oligopeptide or its analog tracer by a particular combination of two protease inhibitors, namely, leupeptin and amastatin. See '041 at column 2, line 64 through column 3, line 15 and column 3, line 61 through column 4, line 6. Thus, the extensive list of protease inhibitors found in Table 1 of '041 demonstrates merely that all of the listed protease inhibitors are ineffective when used alone to suppress the breakdown of osteocalcin 37-49 oligopeptide, but that the particular combination of leupeptin and amastatin in the specific concentrations noted is effective at suppressing such a breakdown. In addition, it is respectfully pointed out that the Examiner is in error in asserting that '041 lists all of the elected species recited in applicants' claim 13 inasmuch as there is no listing of the elected species p-aminobenzamidine. In any event, the Examiner has offered no explanation as to why one of ordinary skill in the art concerned with the removal of proteases from biofluids would look to the disclosure of '041, which is merely concerned with the suppression of the breakdown of osteocalcin 37-49 oligopeptide, and not at all with the removal of proteases.

Applicants also point out that claim 1 has been amended so as to recite that the membrane bodies of the claimed device each "consist essentially of" a functionalized microporous membrane body containing functional groups... and at least one protease inhibitor. This language is submitted to exclude the possibility of the presence of a protease substrate of a crosslinked transferrin/albumin derivative such as is required to be present in the protease activity-measuring membrane of '272. Accordingly, the obviousness rejection of claims 11-15 based upon the combination of '090 with '272 and '041 should be withdrawn.

For the reasons stated, early and favorable reconsideration is respectfully solicited.

Respectfully submitted,



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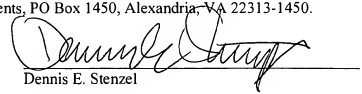

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